

REMARKS

Claims 37-79 are pending in this case. Claims 46, 49, 51-54, 56, 57, 61, and 68-79 have been withdrawn from prosecution, and claims 39, 44, and 67 have been cancelled. Claims 37-43, 45, 47-48, 50, 55, 58-60, and 62-66 have been amended. Support for these amendments can be found, *inter alia*, in the claims as originally filed. After entering this amendment, claims 37, 38, 40-43, 45, 47, 48, 50, 55, 58, and 62-66 will be pending.

The outstanding issues in the final office action are addressed individually below.

1. Claim Rejections Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 38-45, 47-48, 50, 55, 58-60, and 62-66 were rejected under 35 U.S.C. § 112, first paragraph, as not enabling one of skill in the art to make and use the claimed invention. Specifically, the Office Action states that “the dependent claims are still drawn to vaccines and thus contain the same enablement issues as previously presented” (see Office Action, pg. 4).

Applicants have amended the dependent claims to directly recite the language in claim 37, as it was amended in the Supplemental Amendments filed February 6, 2008. Support for these amendments can be found, *inter alia*, in the claims as originally filed, and in the specification on page 10, third paragraph; page 27, fifth paragraph; and Examples 1-21.

Applicants note that the Office Action responded to certain arguments presented in the response filed November 19, 2007. After the filing of that response, Applicants amended the claims in a Supplemental Response filed February 6, 2008 and in this paper to recite “a transdermal antigenic composition.” The arguments set forth in the Office Action responding to the arguments set forth on November 19, 2007 are deemed moot.

Accordingly, Applicants respectfully request that this enablement rejection be reconsidered and withdrawn.

2. Rejections Pursuant to 35 U.S.C. § 103

Claims 37-38, 40-45, 47-48, 50, 55, 58-60, and 62-66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Glenn *et al.* (PCT Publ., WO 98/20734) (“Glenn”) in view of Paul *et al.* (1995) *Vaccine Res.* 4: 145-164 (“Paul”) “for the reasons set forth in the rejection...in the previous office action” (see Office Action, pg. 7). The Office Action sets forth

certain contentions relating to Applicants arguments regarding the enablement of claims drawn to vaccines (see Office Action, pp. 4-6). Applicants respectfully disagree with this rejection.

For a claimed invention to be obvious under 35 U.S.C. § 103, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)). Even if references and/or the knowledge of those of skill in the art teach or suggest all of the limitations of a claim, an obviousness rejection is overcome by a showing of unexpected results (MPEP § 716.02(a); see also *KSR Int'l. Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1740 (2007), citing, *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969) (noting that the *Anderson's* Court found a conclusion that a design was not obvious was supported by evidence showing the elements of the design worked together in an *unexpected* and fruitful manner)). In particular, evidence showing a greater than expected result is persuasive of nonobviousness (see *id.*, citing, *In re Corkill*, 711 F.2d 1496, (Fed. Cir. 1985)). An obviousness rejection is also improper where the references teach away from their combination (MPEP § 2145 X.D.2).

Applicants' invention, as recited in amended Claim 37, is directed to a transdermal antigenic composition. The composition comprises a transdermal carrier comprising a penetrant suspended or dispersed in an aqueous solvent. The penetrant is in the form of a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility. The substances form homoaggregates of one substance and/or heteroaggregates of the at least 2 substances. The average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, is smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher. The elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains. The claim also recites that the composition comprises a compound which specifically has or induces cytokine or anti-cytokine activity and an antigen or mixture of different antigens and/or an allergen or mixture of different allergens. In addition, the

composition contains a chemical irritant, an extract or a compound from a pathogen, a fragment or a derivative of the chemical irritant, or compound isolated from a pathogen.

Paul teaches transfersome compositions that include bovine serum albumin labeled with fluorescein when investigating new avenues for *in vivo* immunization. In particular, Paul teaches the use of these compositions for vaccinations involving full-length proteins across intact skin (see, *e.g.*, pg. 146, ¶ 3). Paul additionally teaches that the use of transdermal compositions alone is sufficient for achieving an adequate vaccination using BSA-FITC antigenic molecules. However, Paul does not teach or suggest that a “chemical irritant and/or an extract or a compound from a pathogen, a fragment or a derivative of the chemical irritant, or compound isolated from a pathogen” is beneficial for obtaining an optimal immunological response to therapeutically relevant antigens. Paul does not teach or suggest the need for additional compounds to co-stimulate an immune reaction (*i.e.*, a compound that induces cytokine or anti-cytokine activity), which, according to the invention, confer certain therapeutic advantages to the claimed composition, including, but not limited to, an increased success in vaccination (see, in the specification, *e.g.*, pg. 11, final ¶). .

Glenn discloses transcutaneous vaccines of tetanus toxoid and IL-12. Glenn also teaches that cholera and its B subunit are each “potent adjuvants for transcutaneous immunization, inducing high levels of IgG but not IgE” when topically applied to the skin of BALB/c mice (see Fig. 1; pg. 20, lines 20-30; see also pg. 7, lines 26-28 (defining an “adjuvant” as an activator of Langerhans cells, which Glenn considers necessary for achieving the described immune response)). Glenn distinguishes itself from Paul by explicitly contrasting its invention from the cited art, of which Paul is one of the references cited by Glenn (pg. 3, line 29). Glenn does not explicitly teach that tetanus toxin and IL-12 are suitable for use in the described system.

As an initial matter, Applicants respectfully disagree with the contentions set forth in the Office Action regarding unexpected results, and with Applicants reading of the MPEP and case law (see Office Action, pg. 8 and 9). Section 716.02(a)(I) is entitled, “Greater Than Expected Results Are Evidence Of Nonobviousness” (MPEP § 716.02(a)(I)). The MPEP cites *In re Corkill* and states that a particular unexpected result “was persuasive of nonobviousness” (see *id.*). Applicants aver that they have not misstated the MPEP.

With regard to the contentions set forth in the Office Action on unexpected results and case law, the case law cited in the Office Action does not stand for the naked principle that unexpected results do not overcome “a strong case of obviousness” (see Office Action, pg. 9). Although it is true that unexpected results must be weighed with all evidence in an obviousness analysis, if unexpected results are commensurate with the claims and are indeed unexpected in view of what was taught in the art, such results would almost certainly establish that the claims were not obvious (see *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969) (the *Anderson's* Court found a conclusion that a design was not obvious was supported by evidence showing the elements of the design worked together in an *unexpected* and fruitful manner)). None of the cases cited in the Office Action disprove this premise. *In re Oetiker* did not rule on this point at all, and *In re Chupp* stands for the proposition that “[t]o be patentable, a compound need not excel over prior art compounds in all common properties” (see 816 F.2d 643, 646 (Fed. Cir. 1987)). In *Chupp*, the panel actually *reversed* a holding of obviousness and held that the unexpected results did not have to excel in all respects over the prior art (see *id.* at 646). In short, neither of these cases establishes the Office Action’s premise that unexpected results do not overcome “a strong showing of obviousness.”

Moreover, *Newell Cos. V. Kenney Mfg. Co.* does not stand for the proposition that “a strong showing of obviousness” should be maintained in the face of a showing of unexpected properties that are commensurate in scope with the claims. *Newell* was decided based on the lack of showing of sufficient evidence of secondary considerations to overcome obviousness. At no point in that decision did the panel mention or specifically describe a showing of unexpected results. In fact, the patentee did not assert *any* unexpected properties. Although *Newell* correctly states that obviousness is an objective inquiry, it does not state that unexpected results that are commensurate with the scope of the claims and are truly unexpected can be overcome by “a strong showing of obviousness” (see *Newell*, 864 F.2d 757, 768 (Fed. Cir. 1988)).

Richardson-Vicks, Inc. v. The Upjohn Co. provides no more support for the proposition asserted in the Office Action than do the other cited cases. In that case, the trial court discounted the showing of unexpected results, not because such results can be overcome by a strong showing of obviousness, but because the alleged property was unknown at the time of invention, and several other groups similarly arrived at the invention without knowledge of the unexpected property (see *Richardson-Vicks, Inc.*, 122 F.3d 1476, 1482 (Fed. Cir. 1997)). In other words, the

unexpected properties were not unexpected, but rather, if the composition had been better understood, the properties would have been expected.

Therefore, the case law cited in the Office Action does not support the proposition that “a strong showing of obviousness” can be maintained in the face of a clear showing that the results of an invention were unexpected. In the previous response, Applicants were not stating or even suggesting that a weighing of the evidence was not necessary. Applicants were merely pointing out that if the technical teachings of the invention provided an experimental result that was at odds with the expectation taught in the art, then such results would overcome an obviousness rejection with the caveat that such result was commensurate with the claims.

Unlike in the cases cited in the Office Action, Applicants respectfully aver that the claimed compositions have yielded unexpected properties over what the cited art cited against the claims in fact teaches was expected—namely, that *immunoadjuvants do not necessarily strengthen the immune response when using transdermal immunization* (see Paul, pg. 155, third para. and pg. 159, first para.). Paul explicitly sets forth that co-stimulatory factors *did not improve the immune response*, and further teaches that such additional factors were actually *unnecessary* to produce an improved, protective immune response (see *id.*). In contrast, Applicants unexpectedly determined that co-stimulatory factors (*i.e.*, compounds that induce cytokine or anti-cytokine activity), in fact, induced an *improved* protective immune response, which *increased the survival rate* of tested animals see (see Specification, Fig. 8). These results clearly demonstrate that *improved* protective immunity can be induced with the addition of co-stimulatory factors to the penetrant composition. Thus, the composition recited in the claims could not have been obvious to the skilled person in the art in view of Paul.

In addition, Applicants assert that Glenn and Paul teach away from each other, and moreover, that Glenn specifically sets itself apart from Paul. Glenn repeatedly touts a particular advantage for its transcutaneous immunization system, namely, that the described immunogenic formulation only needs to be applied directly to the “surface of the skin” to induce a “potent immune response” (Glenn, pg. 14). Glenn attains this immune response due to “delivery of vaccine antigen only to Langerhans cells on the stratum corneum” by means of “passive diffusion and subsequent activation of the Langerhans cells to take up antigen” (see *id.* at 12). To highlight the importance of this advantage, Glenn explicitly refers to Paul at Fig. 1 and notes

that “formulations of antigen in solution, antigen in solution, antigen and mixed micelles, and antigen and liposomes...applied to the skin did *not* induce an immune response *equivalent* to that induced subcutaneous injection” (see *id.* at 1-2, emphasis added). For these reasons, Applicants maintain that one of ordinary skill in the art would not have reasonably combined the teachings provided by these references.

Applicants emphasize that Glenn expressly states that the transdermal carriers of Paul are not necessary or even desired for use in the described transcutaneous immunization system. As stated above, the formulation described in Glenn can be applied *directly* to the skin, thereby to achieve an immune response by passive diffusion and subsequent activation of the Langerhans cells situated in the stratum corneum (see Glenn, pg. 12). In short, Glenn was actively attempting to develop formulations that would *not* require the transfersome formulations taught in Paul. Accordingly, Glenn and Paul teach away from any possible combination that would yield the claimed invention and thus, the person skilled in the art would not fairly combine these disclosures to achieve the subject matter of the claimed invention.

Accordingly, as neither Paul nor Glenn, nor a combination thereof, renders Applicants’ claimed invention obvious, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

Likewise, as dependent Claims 38, 40-45, 47-48, 50, 55, 58-60, and 62-66 contain all of the limitations of amended Claim 37, Applicants respectfully request that their rejection should also be reconsidered and withdrawn.

3. *Claim Rejections Pursuant to 35 U.S.C. § 112, Second Paragraph*

Claims 38, 40-45, 47-48, 50, 55, 58-60, and 62-67 were rejected under 35 U.S.C. § 112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (see Office Action, pg. 15). Specifically, the Office Action states that the claims “recite the limitation ‘vaccine’...[t]here is insufficient antecedent basis for this limitation in the claims” (see Office Action, pg. 15).

Applicants have amended the dependent claims to recite the language in claim 37, as it was amended in the Supplemental Amendments filed February 6, 2008. As such, the claims now

recite the limitation as recited in Claim 37. Furthermore, Applicants have canceled claims 44 and 67 without prejudice, which moot the rejection of these claims.

For these reasons, Applicants respectfully request that this indefiniteness rejection be reconsidered and withdrawn.

4. Claim Rejections under § 102(b)

Claim 37 was rejected as allegedly being anticipated by Paul et al. (1995) *Vaccine Res.* 4: 145-164 (“Paul”). The Office Action alleges that Paul discloses “a transdermal carrier known as a transfersome that comprises ethanolic soybean phosphatidylcholine, sodium cholate, an antigen (BSA), and a compound which induces cytokine activity (lipid A)” (see Office Action, pg. 16). The Office Action further contends that “[s]aid transfersomes have the same composition as the claimed vaccine carrier and would thus necessarily have the same physical and immunological properties as the claimed vaccine transfersomes” (see *id.*). Applicants respectfully disagree with this rejection.

According to MPEP § 2131, a reference must contain *each and every element*, either explicitly or inherently described, as set forth in the claim to be an anticipatory reference. Furthermore, the elements in the reference must be arranged as required by the claim, even if the terminology is not similar (see MPEP § 2131).

As stated above, amended Claim 37, is directed to a transdermal antigenic composition. The composition, in part, comprises a transdermal carrier comprising a penetrant suspended or dispersed in an aqueous solvent, the penetrant being in the form of a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility. In addition, the composition contains a chemical irritant, an extract or a compound from a pathogen, a fragment or a derivative of the chemical irritant, or compound isolated from a pathogen.

Paul teaches transfersome compositions that include bovine serum albumin labeled with fluorescein when investigating new avenues for *in vivo* immunization. Paul does not teach or even suggest that the disclosed composition includes a chemical irritant and/or an extract or a compound from a pathogen, a fragment or a derivative of the chemical irritant, or compound isolated from a pathogen.

Applicants thus respectfully assert that Paul cannot anticipate Claim 37 because Paul fails to provide compositions comprising a chemical irritant, an extract or a compound from a pathogen, a fragment or a derivative of the chemical irritant, or compound isolated from a pathogen. As such, Paul fails to teach *each and every element* of claim 37. Thus, Paul cannot anticipate claim 37.

Accordingly, Applicants respectfully request that this § 102(b) rejection be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on May 1, 2008 have been addressed and should be reconsidered and withdrawn.

The time for responding to this action has been extended to November 1, 2008 by the accompanying Petition for a Three Month Extension of Time and payment of fee. The due date for this response falls on a weekend, and therefore, the filing of this response on November 3, 2008 is timely. No additional fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,

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